

Brugada Syndrome and fever

Dr. Andrés R. Pérez Riera

Since temperature affects permeability, temperature change forces the Na⁺channel and other channels to modify their functional state. I_{Na}⁺ kinetics depends strongly on temperature. (Nagatomo T, Fan Z, Ye B, Tonkovich GS, January CT, Kyle JW, Makielski JC. Temperature dependence of early and late currents in human cardiac wild-type and long Q-T DeltaKPQ Na⁺ channels. *Am J Physiol* 1998; 275:H2016-H2024.) Thus, an increase of 10°C increments the voltage or width by a factor of 1.3 to 1.6 and increases the time of opening and the number of times that the channel is opened by a factor of three. Activation and inactivation kinetics for early I_{Na}⁺ are twofold faster at higher temperature, and shift activation and steady-state inactivation. Then, the fever is considered triggers to PVT/VF in the BrS jointly with other causes that causing modifications in the degree of elevation of the J point and of the ST segment. The other factors capable to get worse the ventricular repolarization are: antimalarial agents; tricyclic antidepressants; class IA (ajmaline and procainamide) and IC (flecainide, pilsicainide) anti-arrhythmic agents; hyperglycemia; nocturnal bradycardia by vagal predominance; alcohol consumption; mental stress and cocaine use.

In BrS, fever is associated with a greater chance of tachyarrhythmic events; this suggests that the increase in temperature affects the Na⁺channel conductance. Mutations in a cardiac sodium channel gene have been linked to this syndrome and some experimental data suggest that the dysfunction of the mutated channel can be temperature sensitive.

Dumaine et al. hypothesized that at more physiological temperatures; the missense mutation may change the gating of the sodium channel such that the net outward current is dramatically augmented during the early phases of the right ventricular AP. The authors tested this hypothesis by expressing Thr1620Met in a mammalian cell line, using the patch-clamp technique to study the currents at 32 degrees C. They concluded that Thr1620Met current decay kinetics are faster when compared with the wild type at 32 degrees C. Recovery from inactivation was slower for Thr1620Met at 32 degrees C, and steady-state activation was significantly shifted. These findings explain the features of the ECG of BrS patients, illustrate for the first time a cardiac I_{Na}⁺ channel mutation of which the arrhythmogenicity is revealed only at temperatures approaching the physiological range, and suggest that some patients may be more at risk during febrile states.

Nagatomo et al characterized early I_{Na}⁺ (the peak and initial decay) and late I_{Na}⁺ of the wild-type hH1 channel and a mutant channel (DeltaKPQ) associated with LQT3. Channels were stably transfected in HEK-293 cells and studied at 23 and 33 degrees C using whole cell patch clamp. Activation and inactivation kinetics for early I_{Na}⁺ were two fold faster at higher temperature for both channels and shifted activation and steady-state inactivation in the positive direction, especially for DeltaKPQ. For early I_{Na}⁺ (<24 ms), DeltaKPQ decayed faster than the wild type for voltages negative to -20 mV but slower for more positive voltages, suggesting a reduced voltage dependence of fast inactivation.

Late I_{Na^+} at 240 ms was significantly greater for DeltaKPQ than for the wild type at both temperatures. The majority of late I_{Na^+} for DeltaKPQ was not persistent; rather, it decayed slowly, and this late component exhibited slower recovery from inactivation compared with peak I_{Na^+} .

Kinetic changes for early and peak I_{Na^+} for DeltaKPQ compared with the wild type at both temperatures were:

- 1) Reduced voltage dependence of steady-state inactivation with no difference in midpoint;
- 2) Positive shift for activation kinetics, and;
- 3) More rapid recovery from inactivation.

There are references of ST-segment elevation, spontaneous T wave alternans, premature ventricular contractions, severe polymorphic ventricular tachycardia with syncope and incessant monomorphic ventricular tachycardia with fatal electrical storm related in febrile states (Nagatomo T, Fan Z, Ye B, Tonkovich GS, January CT, Kyle JW, Makielski JC. Temperature dependence of early and late currents in human cardiac wild-type and long Q-T DeltaKPQ Na^+ channels. *Am J Physiol* 1998;275:H2016-H2024.) (Morita H, Nagase S, Kusano K, Ohe T. Spontaneous T wave alternans and premature ventricular contractions during febrile illness in a patient with Brugada syndrome. *Cardiovasc Electrophysiol*.2002; 13:816-818.) (Porres JM, Brugada J, Urbistondo V, Garcia F, Reviejo K, Marco P. Fever unmasking the Brugada syndrome. *Pacing Clin Electrophysiol*. 2002; 25:1646-1648.) (Dinckal MH, Davutoglu V, Akdemir I, Soydinc S, Kirilmaz A, Aksoy M. Incessant monomorphic ventricular tachycardia during febrile illness in a patient with Brugada syndrome: fatal electrical storm. *Europace*. 2003; 5:257-261.)

Amin et al. (Amin AS, Klemens CA, Verkerk AO, Meregalli PG, Asghari-Roodsari A, de Bakker JM, et al. Fever-triggered ventricular arrhythmias in Brugada syndrome and type 2 long-QT syndrome. *Neth Heart J*. 2010 Mar;18:165-169.) report that the risk for ventricular arrhythmias in BrS and LQT-2 is further increased during fever. Moreover, the authors demonstrate that fever may aggravate coved-type ST-segment elevation in BrS, and cause QTc lengthening in LQT-2. Finally, Amin et al described the molecular mechanisms that may underlie the proarrhythmic effects of fever in BrS and LQT-2.

Additionally, ECG changes typical of BrS can be unmasked during a febrile illness. Then, some BrS patients may display the ECG phenotype only during a febrile state and at normal body temperature, the patient's ECG return to normal (Patruno N, Pontillo D, Achilli A, Ruggeri G, Critelli G. Electrocardiographic pattern of Brugada syndrome disclosed by a febrile illness: clinical and therapeutic implications. *Europace*. 2003; 5:251-255.) (Wakita R, Watanabe I, Okumura Y, Yamada T, Takagi Y, Kofune T, Okubo K, Masaki R, Sugimura H, Oshikawa N, Saito S, Ozawa Y, Kanmatsuse K. Brugada-like Electrocardiographic Pattern Unmasked by Fever. *Jpn Heart J*. 2004; 45:163-167.)

Wakita et al (Wakita R, Watanabe I, Okumura Y, Yamada T, Takagi Y, Kofune T, Okubo K, Masaki R, Sugimura H, Oshikawa N, Saito S, Ozawa Y, Kanmatsuse K. Brugada-like Electrocardiographic Pattern Unmasked by Fever. *Jpn Heart J*. 2004; 45:163-167.) had evidenced that SCN5A-H681P mutation (a single amino acid substitution (H681P) in the SCN5A gene) induces a significant loss of transmembrane current and is clinically associated with a pathologic phenotype that is elicited by hyperthermia.

Matsubara et al (Matsubara E, Fujisaki T, Minamoto Y, et al. Brugada syndrome occurring after autologous peripheral blood stem cell transplantation for acute myeloid leukemia *Rinsho Ketsueki*. 2004; 45:481-483.) showed a case of old man that BrS was unmasked by febrile neutropenia on the 8th day after undergoing high dose chemotherapy followed by autologous peripheral blood stem cell transplantation (ABSCT)

Brugada syndrome, competitive athletic activities and body temperature

Candidates should not participate in competitive athletic activities, considering the possibility that intense training and competitions increase SCD risk. On the other hand, the group of the Brugada brothers states that in this condition, there is no increased risk during strenuous sports activities. The point of view is not to restrict exercise to BS carriers. Effort increases sympathetic tone, which improves repolarization as demonstrated by Guevara Valdívía et al from Mexico, in patients who were BS carriers during the stress test (Guevara-Valdivia ME, Iturralde Torres P, de Micheli A, et al. *Electrocardiographic changes during stress test in a patient with "Brugada syndrome"* *Arch Cardiol Mex*. 2001; 71:66-72.) (Guevara Valdívía ME. Iturralde Torres P, de Micheli A, et al. *Electrocardiographic alterations during exercise stress testing in the "Brugada Syndrome"*. SYMPOSIUM ABOUT THE BRUGADA SYNDROME: TEN YEARS OF HISTORY: 1992/2002.)

In sports that demand extreme efforts that could potentially lead to fatigue, in hot environments, heat dispersion produced as a product of metabolism during exercise is not dispersed efficiently by skin convection, radiation and evaporation. Thus, it can lead to hyperthermia, a factor that is well known to worsen repolarization in BS. In case of dehydration or in a lower efficacy of the sweat glands, an increase of internal body temperature can be observed, what theoretically could worsen repolarization in BS.

Currently, the information is scant on BS and sports. Progressive hyperthermia that can be caused by an intense physical activity in a room not properly ventilated, theoretically could increase body temperature and thus worsen ventricular repolarization, making onset of tachyarrhythmic events in phase 2 easier. During rest, body temperature is near 37 degrees (99F), and during exercise, when the organism is incapable of dispersing heat as fast as it is produced (by conduction, convection, radiation and mostly by evaporation, which is the most important one) a normal person can reach a temperature near the 40 degrees (104F), and muscles can reach 42 degrees (107.6F), activating thermo receptors that via hypothalamus cause vasodilatation and sweat. In concomitance of a hot and humid environment with low speed of air and poor thermal radiation, mostly if there is also dehydration, hyperthermia can extend and cause a tendency to arrhythmias. This effect could be counterbalanced by a higher presence of circulating catecholamines. It is different in hyperthermia of infectious states, where catecholamines increase is not observed. We think that with the evidence available until the present time, the recommendation should be being cautious with letting patients practice competitive sports in BS, since we don't have enough bibliography, postures are conflicting, and intimate pathophysiologic mechanisms during exercise are not yet conveniently clear. On the other hand, from the ethic-legal point of view, we don't have a reply to protect appropriately the health of these patients and ourselves as physicians.

The genetic background of BrS patients sensitive to fever is heterogeneous. Experimental data suggest that the clinical manifestations of fever-exacerbated BrS may not be mutation specific. Four male patients with typical BrS ST-segment elevation in V1-V3 or ventricular arrhythmias during fever were screened for mutations in the SCN5A gene. Wild-type (WT) and mutant Na(v)1.5 channels were expressed in HEK293 cells. The Na⁺ currents were

analyzed using the whole-cell patch clamp technique at various temperatures. Protein expression of WT and mutant channels was studied by Western blot experiments. Two mutations in SCN5A, L325R and R535X, were identified. Expression of the two mutant Na(v)1.5 channels in HEK293 cells revealed in each case a severe loss-of-function. Upon the increase of temperature up to 42 degrees C, the authors observed a pronounced acceleration of Na(v)1.5 activation and fast inactivation kinetics. Cardiac action potential (AP) modeling experiments suggest that in patients with reduced I(Na), fever could prematurely shorten the AP by virtue of its effect on WT channels. Further experiments revealed that L325R channels are likely misfolded, since their function could be partially rescued by mexiletine or curcumin. In co-expression experiments, L325R channels interfered with the proper function of WT channels, suggesting that a dominant negative phenomenon may underlie BrS triggered by fever. (Keller DI, Rougier JS, Kucera JP, et al. *Brugada syndrome and fever: Genetic and molecular characterization of patients carrying SCN5A mutations. Cardiovasc Res.* 2005 ;67: 510-519.).

The elevated body temperature in patients with BrS, cause spontaneous ST elevation leading to fatal ventricular arrhythmias. (Aramaki K, Okura H, Shimizu M. *Chest pain and ST elevation associated with fever in patients with asymptomatic Brugada syndrome Fever and chest pain in Brugada syndrome. Int J Cardiol.* 2005;103:338-339.).

Burrell et al. (Burrell C, Reddy S, Haywood G, Cunningham R. *Cardiac arrest associated with febrile illness due to U.K. acquired Cyclospora cayetanensis. J Infect.* 2007; 54:13-15.) reported a 43 yr old man diagnosed with U.K. acquired cyclospora cayetanensis infection resulting in fever and diarrhea. In course of the febrile illness, he suffered an out of hospital cardiac arrest. Extensive cardiac investigation including a transthoracic echocardiogram, coronary angiogram, and cardiac electrophysiological studies failed to identify the cause. Fever has been reported as a precipitant for idiopathic ventricular fibrillation in patients with the BrS but also rarely in individuals with normal hearts. Clinicians should be aware of a possible link between any febrile illness and potentially fatal ventricular dysrhythmia.

Labra González et al (Labra González R, Casares Medrano J, Sánchez Castaño AJ, López Sánchez FA. *Asymptomatic Brugada syndrome unmasked by influenza virus subtype H1N1 infection. Med Clin (Barc).* 2010 Mar 17. [Epub ahead of print]) presented a case of asymptomatic BrS unmasked by influenza virus subtype H1N1 infection. Tsarouhas et al (Tsarouhas K, Papalexis P, Kafantaris I, Tsitsimpikou Ch, Vavetsi S, Rentoukas E. *Electrocardiographic findings compatible with Brugada syndrome in a patient with febrile respiratory infection. Hippokratia.* 2010 Jul; 14 :221-223.) presented a 57-years-old asymptomatic patient with febrile respiratory infection (39°C). The ECG were Brugada type 1 pattern that gradually turned to Brugada type 2 and 3, following fever remission, and finally became normal. Procainamide provocation test were negative for BrS. Echocardiographic evaluation, treadmill stress test, Holter recording were normals. In patients aged ≤16 years with genetically-confirmed loss-of-function sodium channelopathies presenting with cardiac symptoms, positive family-history and/or abnormal type 1 BrS ECG, and/or prolonged PR interval/QRS duration, fever and

vaccination are potential arrhythmia-triggers; conduction delay is the commonest finding on ECG. Beta-blockers have a role in preventing tachycardia-induced arrhythmias. (Chockalingam P, Clur SA, Breur JM, Kriebel T, Paul T, Rammeloo LA, Wilde AA, Blom NA. The Diagnostic and Therapeutic Aspects of Loss-of-Function Cardiac Sodium Channelopathies in Children. Heart Rhythm. 2012 Aug 7. [Epub ahead of print])